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Attorney's Docket No.: 2139-11US - CC/lcl

~~TECH CENTER 1600/2900~~

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Yasuo KONISHI et al.

Serial No.: 09/529,232 Art Unit.: 1655

Filed: April 10, 2000 Examiner: Janelle TAYLOR

For: TRIVALENT THROMBIN INHIBITOR



**INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 C.F.R. § 1.97 and 1.98**

Assistant Commissioner for Patents

**BOX : INFORMATION DISCLOSURE STATEMENT**

Washington, DC 20231

U.S.A.

Sir:

Submitted herewith on form PTO-1449 is a listing of documents known to applicants in order to comply with applicant's duty of disclosure pursuant to 37 C.F.R. § 1.56. Copies of the listed documents are also being submitted herewith to comply with the proviso of 37 C.F.R. § 1.97 and 1.98, with copies of English translations of non-English language references or of the pertinent portions thereof, if such translations are readily available. If applicable, English copies of foreign search reports citing at least some of the documents herein listed on PTO-1449 are also enclosed.

The references included herewith have been cited in the specification of the instant application.

The submission of any document which is not a statutory bar is not intended as an admission that any or all documents constitute prior art against the claims of the present application. Applicants do not waive any right to take any action that would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a prima facie prior art reference against the claims of the present application.

Statement of relevancy

The listed document is being submitted either in compliance with 37 C.F.R. 197(b), within three (3) months of the filing date of a national application or of the date of entry of the national stage in an international application; or pursuant to 37 C.F.R. §1.97(e)(1), within three (3) months from the date of an office action or of a search report issued in a foreign counterpart application citing each of the documents contained in the present statement; or pursuant to 37 C.F.R. §1.97(e)(2), within three (3) months from the first knowledge of each submitted document by any individual designated in C.F.R. §1.56(c), when each such document was not cited in a communication from a foreign patent office in a counterpart foreign application.

In the case of submissions under 37 C.F.R. §1.97(e)(1) and (2), the undersigned Attorney/Agent of Record hereby certifies that the enclosed references are hereby submitted within three months (1) from the issuance of the foreign action or search report, or (2) from said first knowledge, respectively.

We enclose herewith a cheque in the amount of \$180.00 to cover payment of Submission of an Information Disclosure Statement as prescribed in 37 C.F.R. 1.17(p).

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. 1.17(p) that may be required by this paper, and to credit any overpayment to Deposit Account No. 19-5113.

Respectfully submitted,

March 25, 2003

Date

  
Christian Cawthorn  
Registration No. 47,352

OGILVY RENAULT  
1981 McGill College, Suite 1600  
Montréal (Québec) H3A 2Y3  
CANADA  
Tel.: (514) 847-4256

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Substitute for form 1449A and B/PTO				Complete if Known	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> <i>(use as many sheets as necessary)</i>				Application Number	09/529,232
				Filing Date	APRIL 10, 2000
				First Named Inventor	Yasuo KONISHI et al.
				Art Unit	1655
				Examiner Name	Janelle TAYLOR
Sheet	1	of	3	Attorney Docket Number	

## U.S. PATENT DOCUMENTS

## FOREIGN PATENT DOCUMENTS

Examiner Signature		Date Considered	
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\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

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Substitute for form 1449A and B/PTO

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

(use as many sheets as necessary)

Sheet **2** of **3****Complete if Known**

Application Number	09/529,232
Filing Date	APRIL 10, 2000
First Named Inventor	Yasuo KONISHI et al.
Art Unit	1655
Examiner Name	Janelle TAYLOR

Attorney Docket Number **2139-11US - CC/Icl****OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T <sup>2</sup>
1	1	Giancarlo AGNELLI et al., "Effects of Hirudin and Heparin on the Binding of New Fibrin to the Thrombus in t-PA Treated Rabbits", <i>J. Thrombosis and Haemostasis</i> <b>66</b> , 592-597, 1991;	
2	2	Paul BOURDON et al., "Structure-function relationships of hirulog peptide interactions with thrombin", <i>FEBS Lett.</i> <b>294</b> , 163-166, 1991;	
3	3	John DIMAIO et al., "Bifunctional Thrombin Inhibitors Based on the Sequence of Hirudin <sup>45-65**</sup> ", <i>J. Biol. Chem</i> <b>265</b> , 21698-21703, 1990;	
4	4	"Simple Inhibition Systems", <i>Enzyme Kinetics: Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems</i> , pp 100-160, John Wiley & Sons, 1975;	
5	5	J.M. MARAGANORE et al., "Design and Characterization of Hirologs: A Novel Class of Bivalent Peptide Inhibitors of Thrombin", <i>Biochemistry</i> <b>29</b> , 7095-7101, 1990;	
6	6	John F. MORRISON et al., "The Behavior and significance of slow-binding enzyme inhibitors", <i>Adv. in Enzymol.</i> <b>61</b> , 201-301, 1998;	
7	7	James C POWERS et al., "Synthetic Substrates and inhibitors of thrombin", <i>Thrombin: Structure and Function</i> , Chpater 4, (1992) Lawrence J. Berliner, Plenum Press, New York;	
8	8	Stuart R. STONE et al., "Kinetics of the Inhibition of Thrombin by Hirudin", <i>Biochemistry</i> <b>25</b> , 4622-4628, 1986;	
9	9	Zbigniew SZEWCZUK et al., "Design of a Linker for Trivalent Thrombin Inhibitors: Interaction of the Main Chain of the Linker with Thrombin", <i>Biochemistry</i> , <b>32</b> , pp. 3396-3404, 1993 (No. XP-002067819);	
10	10	Zbigniew SZEWCZUK et al., "Conformationally Restricted Thrombin Inhibitors Resistant to Proteolytic Digestion", <i>Biochemistry</i> <b>31</b> , 9132-9140, 1992;	
11	11	F.B. TAYLOR et al., "Protein C Prevents the Coagulopathic and Lethal Effects of <i>Escherichia coli</i> Infusion in the Baboon" <i>J. Clin. Invest.</i> , <b>79</b> , pp. 918-25, 1987;	

Examiner Signature		Date Considered	
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<sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> Applicant is to place a check mark here if English language Translation is attached.

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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> <i>(use as many sheets as necessary)</i>				Application Number	09/529,232
				Filing Date	APRIL 10, 2000
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Sheet	3	of	3		

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\*EXAMINER; Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> Applicant is to place a check mark here if English language Translation is attached.

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>2139-11 PCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/CA 97/ 00745</b>	International filing date (day/month/year) <b>15/10/1997</b>	(Earliest) Priority Date (day/month/year)
Applicant <b>NATIONAL RESEARCH COUNCIL OF CANADA et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1.  Certain claims were found unsearchable (see Box I).
2.  Unity of invention is lacking (see Box II).
3.  The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
  - filed with the international application.
  - furnished by the applicant separately from the international application,
    - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
    - Transcribed by this Authority
4. With regard to the title,  the text is approved as submitted by the applicant.
  - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
  - the text is approved as submitted by the applicant.
  - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is:
 

Figure No. \_\_\_\_\_

  - as suggested by the applicant.
  - because the applicant failed to suggest a figure.
  - because this figure better characterizes the invention.
  - None of the figures.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 97/00745

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 13 and 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 97/00745

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 C07K14/815 A61K38/58

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	<p>SZEWCZUK E.A.: "Design of a linker for trivalent thrombin inhibitors; interaction of the main chain of the linker with thrombin"  <b>BIOCHEMISTRY</b>,          vol. 32, no. 13, 6 April 1993, EASTON, PA US,          pages 3396-3404, XP002067819          see the whole document</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-4,7-14

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 June 1998

Date of mailing of the international search report

15. 07. 1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Groenendijk, M

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 97/00745

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TSUDA E.A.: "Design of potent bivalent thrombin inhibitors based on hirudin sequence: incorporation of nonsubstrate-type active site inhibitors" BIOCHEMISTRY, vol. 33, no. 48, 6 December 1994, EASTON, PA US, pages 14443-14451, XP002067820 see the whole document -----	1-4,7-14
Y	WO 95 11921 A (NAT RESEARCH COUNCIL CANADA NR ;KONISHI YASUO (CA); SZEWCZUK ZBIGN) 4 May 1995 see the whole document -----	1-4,7-14
A	KRISHNAN: "Synthesis, structure and structure-activity relationships of divalent thrombin inhibitors containing an alpha-keto-amide transition-state mimic" PROTEIN SCIENCE, vol. 5, no. 3, March 1996, pages 422-433, XP002067821 -----	1-14

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/CA 97/00745

Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
WO 9511921 A	04-05-1995	AU 7935494 A	2175388 A	0725797 A	22-05-1995 04-05-1995 14-08-1996